REMARKS

I. Status of the Claims

Claims 1, 2 and 4-36 are pending, claims 18 and 19 having been withdrawn by the Examiner. Accordingly, claims 1, 2, 4-17 and 20-36 are pending and at issue.

Applicants thank the Examiner for the careful consideration of this application. Reconsideration of the present application is respectfully requested in view of the remarks below.

II. Rejections Under 35 U.S.C. § 103

A. Illum in view of Grebow

Claims 1-2, 4-9, 12, 14-17 and 20-36 stand rejected as obvious over U.S. Patent No. 6,387,917 issued to Illum et al. (hereafter "Illum"), in view of U.S. Patent No. 5,026,825 issued to Grebow et al. (hereafter "Grebow").

Applicants have previously noted that there would have been no reasonable expectation of successfully incorporating the antimicrobial agents in Grebow's calcitonin formulation into the morphine formulations disclosed in Illum to provide a stable formulation. For at least this reason, a *prima facie* case of obviousness has not been established. In response, the Examiner asserts:

> The Examiner respectfully disagrees. Illum discloses [that] his nasal formulation can comprise antimicrobial agents. Grebow is relied on for the inclusion [of] specific, art recognized, antimicrobial agents suitable for use in nasal formulations. The relevance of the [Δ-]aminolevulinic acid to the rejection discussed above is unclear to the Examiner. Clarification of how the antimicrobial agents would be unsuitable for use in other nasal formulations is requested.

(Office Action at 5). Applicants appreciate the Examiner's remarks and request consideration of th following remarks.

Applicants note that, in general, morphine formulations have encountered stability problems. *See, e.g.*, FDA Recall # D-581-2101 of Embeda (morphine sulfate and naltrexone hydrochloride, Extended Release capsules), http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm214953.htm. While it is acknowledged that Illum itself does not disclose stability problems with its product, a person of ordinary skill in the art would nevertheless be wary of incorporating additional elements into morphine formulations due to problems of morphine stability in general. While Grebow does mention antimicrobial agents, such antimicrobial agents are combined with calcitonin, and analogs thereof -- not morphine.

The Examiner has requested that applicants clarify the relevance of Δ-aminolevulinic acid in Grebow. Δ-aminolevulinic acid is an additive in Grebow that is employed to prevent degradation of the active agent. In this regard, Δ-aminolevulinic can be viewed as an agent that increases the stability of the calcitonin, at least upon being administered to a patient. The long-term effect of incorporating antimicrobial compositions in Grebow, without Δ-aminolevulinic acid, is unknown. This is relevant because Illum's formulations do not contain an agent like Δ-aminolevulinic acid to maintain the integrity of the morphine active agent, and morphine decomposition products could contribute to the stability problems of morphine formulations.

Thus not only does Illum employ an active agent (morphine) that is known to present stability problems in other formulations, but it also does *not* incorporate adjuvants, like Δ-aminolevulinic acid, to prevent the degradation of the morphine into decomposition products (which are themselves thought to contribute to stability problems). Accordingly, one of ordinary

skill in the art would have no reasonable expectation of successfully combining morphine and an antimicrobial agent to provide a stable product. Applicants respectfully request that the obviousness rejection be withdrawn.

B. Illum in view of Grebow, further in view of Tulin; Illum in view of Grebow, further in view of Santus

Claim 11 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 5,508,282 issued to Tulin-Silver et al (hereafter "Tulin"). Tulin is cited only for its teaching of ascorbic acid or sodium ascorbate. Applicants have previously noted that Tulin does not overcome the deficiencies noted above with respect to Illum and Grebow. After consulting Tulin, there still would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation.

Claim 13 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 6,333,044 issued to Santus et al (hereafter "Santus"). Santus is cited only for its teaching of sodium benzoate. Applicants have previously noted that Santus does not, overcome the deficiencies noted above with respect to Illum and Grebow. After consulting Santus, there still would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation. In this regard, it is noted that Santus relates to intranasal formulation containing Ketorolac®, as opposed to morphine, which is known to present stability concerns.

In response to these arguments, the Examiner asserts:

> Applicant has provided no evidence that the antimicrobial agents or antioxidants contribute to the stability of the formulation or that the formulation of Illum is unstable. Applicant has not provided any evidence that the specific use of the claimed antimicrobial agents and antioxidants provide any unexpected results over what would be expected as a functional equivalent.

(Office Action at 7). Applicants request reconsideration in view of the following remarks.

Applicants acknowledge that data comparing the stability of morphine formulations with and without an antimicrobial agent selected from benzalkonium chloride, disodium EDTA, or a combination thereof has not been made of record. Furthermore, Applicants acknowledge that there is no evidence in the disclosure of Illum that its formulations are unstable. Applicants respectfully submit however, that such evidence is not required given that the Examiner has failed to first establish a *prima facie* case of obviousness, which as discussed above is based on known stability problems of morphine formulations in general, and the lack of specific agents in Illum intended to prevent the degradation of the morphine. It is only upon establishing a *prima facie* case of obviousness when the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case, such as the comparative data referenced above by the Examiner. *See*, MPEP § 2145, *citing*, *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

At least because there would have been no reasonable expect of successfully incorporating the antimicrobial agents of Grebow into the morphine formulations of Illum, a *prima facie* case of obviousness has not been established. Inclusion of the additional secondary references cited by the Examiner, i.e., Tulin and Santus, does not overcome this deficiency. Accordingly, Applicants respectfully request that the obviousness rejections be withdrawn and the application passed to issuance.

Conclusion

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections. Applicants further submit that the application is now in condition for allowance, and they earnestly solicit timely notice of the same. Should the Examiner have any questions, comments or suggestions in furtherance of the prosecution of this application, the Examiner is invited to contact the attorney of record.

Applicants submit herewith a Request for Continued Examination (RCE), and the fee associated therewith. Should the Commissioner deem that any additional fees are due, the Commissioner is authorized to debit Baker Botts L.L.P. Deposit Account No. 02-4377, Order Number 077350.0235 for any additional fees that may be due in association with this filing.

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Respectfully submitted,

By _____
Jason C. Chumney
Registration No.: 54,781

Baker Botts L.L.P.
30 Rockefeller Plaza
44th Floor
New York, NY 10112-4498
(212) 408-2500
(212) 408-2501 (fax)

Attorneys/Agents For Applicant